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13. SUPPLEMENTARY NOTES

14. ABSTRACT During this sixth year of the project, we have successfully completed Institutional Review Board approval from the University of Pittsburgh and USAMRMC Human Research Protection Office. We proceeded with training of the key personnel needed for implementation of the protocol. The training included several animal studies, examination of a cadaver, and "dry runs" using full-scale human simulators at the Winter Institute for Simulation Education and Research. Trainees included trauma surgeons, cardiothoracic surgeons, perfusionists, Emergency Department personnel, and research staff. We acquired the equipment that will be needed in the Emergency Department. As of April, 2014, the staff of the trauma center at UPMC Presbyterian have been prepared for study enrollment. No appropriate candidates have been identified yet. We are reviewing the data on patients who have undergone Emergency Department thoracotomies during this time to better understand why enrollment has been less than expected. As of June, 2013, Dr. Tisherman has moved to the Shock Trauma Center at the University of Maryland. This center already has approval from its IRB for community consultation. Dr. Tisherman is working with the research staff to implement this plan in the near future.

15. SUBJECT TERMS
Trauma, hemorrhagic shock, cardiac arrest, cardiopulmonary resuscitation, hypothermia

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Introduction

Cardiopulmonary resuscitation (CPR) can save victims of normovolemic cardiac arrest (CA), e.g., ventricular fibrillation. During exsanguination CA from trauma, however, CPR, even with an emergency department (ED) thoracotomy and open chest CPR, results in unacceptably low survival rates. *Emergency Preservation and Resuscitation (EPR)* was developed to rapidly preserve the organism during ischemia, using hypothermia, drugs, and fluids, to "buy time" for transport and resuscitative surgery. The purpose of this study is to test the feasibility of rapidly inducing profound hypothermia ($\leq 10^{o}C$) with an aortic flush in trauma victims that have suffered CA and failed standard resuscitative efforts to enable resuscitative surgery and delayed resuscitation with cardiopulmonary bypass. The primary outcome variable will be survival to hospital discharge with minimal neurologic dysfunction.

Body

Scientific Progress

In December, 2009, we conducted the first meeting of the Data and Safety Monitoring Board. The group approved moving forward with the study. They recommended standardization of the transfusion protocols across sites, elimination of blunt trauma victims, and the use of Seldinger technique for aortic cannulation. In subsequent meetings, they have also asked for more prolonged follow-up of subjects (to 12 months), including additional functional outcome using the SF-36 form. They further recommended that the trauma surgeons involved in the study obtain hospital privileges for cannulation for the EPR flush. This has been accomplished.

Given the complexity of our planned intervention for trauma patients in cardiac arrest, we need to optimize subject inclusion and exclusion criteria. The literature on such patients is scant, with studies focusing on mortality rates and crude information such as signs of life (pulse, breathing, spontaneous movements) in the field or emergency department and admission cardiac rhythm. To better define this patient population to optimize subject selection, we have initiated a retrospective study to look at other factors that could be quickly determined during the resuscitation of a trauma patient in the emergency department. This retrospective study should produce publishable data, although so far we have not obtained sufficient data to make any conclusions. We will initiate a similar study at the University of Maryland.

Separately, to better profile patients who die from trauma, Dr. Tisherman led a study of the hemorrhagic shock database of the Resuscitation Outcomes Consortium, which studies prehospital care in patients with life-threatening injuries. Within this database, we have identified 67 patients with hemorrhagic shock and no significant head injury who died within 24 hours of their injuries. These patients represented 83% of all deaths in the shock cohort. The primary cause of these early deaths was indeed hemorrhage. Twenty-six patients died in the Emergency Department. Data on timing of pulselessness and use of ED thoracotomies is not available in the database. Presumably, many of these patients could have been EPR candidates. Overall, this dataset suggests that the great majority of deaths from traumatic hemorrhage occur within 24 hrs from direct effects of hemorrhage. Late deaths are rare. To improve survival from traumatic hemorrhagic shock, early, novel interventions, such as EPR, are needed.

Administrative and Logistic Matters

The first regulatory step for proceeding with this study was to obtain an Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA). Our trial is complicated by the fact that both fluids and equipment are to be used for an application that is not currently approved by the FDA. We have now obtained an investigator-sponsored IDE from the FDA Center for Devices and Radiological Health Office of Device Evaluation.

With the approval of the IDE, we were able to obtain approval for the proposal from the University of Pittsburgh Institutional Review Board (IRB) as both the coordinating center and participating site. We have now completed the community consultation and public disclosure processes. These included the meetings with the Pittsburgh Human Relations Commission and the University of Pittsburgh Center for Minority Health, a random-digit telephone survey, surveys in trauma clinic, town hall meetings at the University Student Union, a website, and publicity in local and national media. The results were presented to the IRB and IRB approval has been granted. We have also obtained human use approval from the USAMRMC.

Similarly, the University of Maryland IRB has preliminarily approved the study pending completion of the community consultation process. Other centers that have been identified for possible inclusion in the study in the future include the University of Arizona, Oregon Health and

Sciences University, and the University of Colorado. Until both the University of Pittsburgh and the University of Maryland are actively enrolling, we will not consider initiating these sites.

Because Drs. Tisherman and Kochanek are co-authors of a submitted patent for EPR Methods, the University of Pittsburgh Conflict of Interest Committee reviewed the plans for the trial and defined a plan to resolve the conflict so that these researchers could still be involved in the study.

Key Research Accomplishments

The most important accomplishments this past year have been completion of all training and credentialing of the trauma surgeons who will be involved in initiating EPR. Training of the perfusionists and research staff has also been completed. The UPMC Presbyterian trauma service has been open for enrollment since April, 2014.

We have continued to work on gathering the necessary historical data for the study.

Reportable Outcomes

Despite being ready for enrollment, the University of Pittsburgh has not enrolled any subjects to date.

Conclusion

Most of the work so far on this project has been focused on the regulatory and training processes. We have an IDE and approval from 2 IRBs. We also have successfully conducted animal training sessions and a simulation training session. We have completed the logistics for equipment and personnel to implement EPR in the Emergency Department of UPMC Presbyterian, which is now ready for patient enrollment when an appropriate candidate is identified.

References

None